REMARKS

Claims 1-7, 14-18, 38-50, 60-61, and 67-68 are pending. Claim 65 has been cancelled by the above amendment.

Support for the amendment to claim 1 is found in the specification and claims as originally filed. For example:

- support for "selecting a plurality of variable positions in said ensemble of related protein backbone structures" is found at least in Example 2 (page 29, line 21 *et seq.*) and Figure 8;
- support for "selecting a set of amino acids to computationally test at each of said variable positions in said backbone structures" is found at least in Example 2 (page 29, line 21 *et seq.*), Figure 8 and originally filed Claim 1;
- support for "applying to each protein backbone structure in said ensemble of related protein backbone structures a protein design algorithm to generate at least one variant protein sequence for each of said protein backbone structures" is found at least in Example 2 (page 29, line 21 *et seq.*) and Figure 2 object number 52 and 54, and the paragraph beginning at page 16, line 28;
- support for "substituting each amino acid in said set of amino acids at each variable position in each variant protein sequence" is found at least in Example 2, Table 1, Figure 2 object number 56, and the paragraph beginning at page 17, line 13;
- support for "evaluating the energetic fitness of each amino acid in said set of amino acids at each of said variable positions in each of said variant protein sequences" is found at least in Example 2, Table 1, Figure 2 object number 56, and the paragraph beginning at page 17, line 13; and
- support for "generating a probability matrix by combining said energetic fitness of each of said amino acids in each of said variant protein sequences for each of said protein backbone structures in said ensemble of related protein backbone structures to

generate a total probability for each of said amino acids" is found at least at page 17, line 13 to page 19, line 14.

Telephonic Interview of February 16, 2006

The Applicant thanks Examiner Moran for the courtesy of the telephonic interview conducted on February 16, 2006. During this discussion, the Applicant and his representatives pointed to support for the amendments to claim 1 and for extant language in claim 48 (as further described below). The Applicant also explained how the method of claim 1 differed from the cited MAYO patent. For example, the method of claim 1 uses information derived from the different structures of the ensemble to generate a probability matrix, whereas MAYO does not teach or suggest such a method. The Applicant's position is further elaborated below.

Rejection of Claim 1 under 35 U.S.C. § 112 ¶ 1

The Examiner rejected claims 1 and 65 under 35 U.S.C. § 112 ¶ 1 as being indefinite. Claim 65 has been cancelled, rendering rejection of this claim moot.

The Examiner stated that claim 1, as written, failed to recite a relationship between the first and second steps. Claim 1 has been amended to clarify the connection between the ensemble of related protein backbone structures and each step additional step until the generation of the probability matrix.

Rejection of Claims 39-40 under 35 U.S.C. § 112 ¶ 2

The Examiner rejected claims 39-40 as failing to comply with the written description requirement. The Applicant disagrees, but in the interest of expediting prosecution amends claims 39 and 40 to delete the phrase "and synthesizing."

Rejection of Claim 48

The Examiner rejected claim 48 for lack of support for "a desired property." Support and examples of such properties can be found, e.g., at page 29, lines 28-31 of the specification.

Rejection of Claims under § 102 as anticipated by MAYO

The Examiner stated:

> **MAYO teaches a computerized method wherein an ensemble of backbone structures derived from a naturally occurring protein is provided....**

Applicants respectfully disagree with this characterization of MAYO. MAYO used **unrelated** backbone structures and used each one of them **individually** rather than as an ensemble. In other words, in each run of the program in MAYO, only a single backbone is used to generate the probability matrix. The program in MAYO can be repeated with a different backbone structure, but the results of the second structure are not used in conjunction with the first structure to generate a single probability matrix. Thus, MAYO does not teach using multiple related backbone structures as input in one simulation. Information from the backbone structures is not combined to produce a probability matrix.

In the method of claim 1, the probability matrix is generated by using information from all the structures in the ensemble of backbone structures, as recited in the step of "generating a probability matrix by combining said energetic fitness of each of said amino acids in each of said variant protein sequences for each of said protein backbone structures in said ensemble of related protein backbone structures to generate a total probability for each of said amino acids." MAYO does not teach the use of an ensemble of related protein backbone structures as input to generate a probability matrix. In particular, since MAYO does not combine energetic fitness of amino acids at different positions in different structures in an ensemble, MAYO cannot anticipate amended claim 1.

Additionally, the method of amended claim 1 includes "substituting each amino acid in said set of amino acids at each variable position in each variant protein sequence." Although MAYO allegedly teaches the generation of a plurality of sequences, it does not provide a method for evaluating each amino acid in said set. For instance, possible variant amino acids in a set would be absent where the possible variant amino acid does not appear at a variant position in at least one variant sequences. MAYO does not evaluate each amino acid in said set. Thus, the probability matrix of MAYO does not provide a probability for each amino acid in a set of amino acids at every variable position. See, e.g., Table 1 of the instant application.

As seen, MAYO does not teach or suggest combining energetic fitness information for an "ensemble of related backbone structures," nor "substituting each amino acid in said set of amino acids at each variable position in each variant protein sequence" as required by the method of amended claim 1. Accordingly, MAYO cannot anticipate this claim. The remaining claims depended from claim 1, and are thus patentable for at least these reasons.

Obviousness Rejection of claims 7, 14, 18, 38-47 and 49-50 citing MAYO and KOEHL

The Examiner stated:

> **KOEHL teaches a computerized method of generating a global conformational (probability) matrix representing a protein structure (p. 250) wherein a self consistent mean field theory/algorithm (SCFM) is used to generate possible side chain sequences and to evaluate fitness (potential energy) of all possible rotamers to generate a matrix (pp. 251-252 and 256-257).**

The Applicant respectfully disagrees with this characterization of KOEHL because KOEHL does not teach the generation of "possible side chain sequences." Rather, KOEHL teaches the prediction of conformation of known side chains using a known starting sequence. All that KOEHL purports to teach is predicting a rotamer for a known side chain. Thus, on page 250, KOEHL states "the final matrix provides the probabilities of all possible positions for all side chains of the protein." This final matrix does not provide the probability that another amino acid could be located at a given position. In contrast, the method of claim 1 provides a probability matrix that indicates the probability that an amino acid can occupy a particular position in a ensemble of structures.

As stated above, MAYO does not teach or suggest every limitation of amended claim 1. Additionally, the method of claim 1 differs substantially from KOEHL. These differences include at least three limitations of claim 1: first, the provision of an ensemble of related protein backbone structures as input to the program; second, substituting each amino acid in said set of amino acids at each variable position in each variant protein sequence; and, third, generating a probability matrix by combining said energetic fitness of each of said amino acids in each of said variant protein sequences for each of said protein backbone structures in said ensemble of related protein backbone structures to generate a total probability for each of said amino acids. MAYO does not supply these missing elements.

Protein design differs substantially from predicting the structure of a given primary sequence. A protein design algorithm generates amino acid sequences (typically new amino acid sequences) that satisfy a particular characteristic, e.g., ability to form a particular three-dimensional fold. In a method of protein design, the amino acid sequence is the **unknown**. The input for the method is often a desired three-dimensional fold; the output is one or more amino acid sequences that are predicted to adopt the desired fold.

In contrast, structure prediction relies on a **known** amino acid sequence as its input and produces, as its output, a prediction of side chain conformations for the amino acid sequence. Structure prediction does not generate an amino acid sequence, quite the contrary, an amino acid sequence is the prerequisite for structure prediction. These marked differences not only make KOEHL inapplicable, but also negate any motivation to combine MAYO with KOEHL.

Neither MAYO nor KOEHL discloses "an ensemble of related protein backbone structures as input into said program," or "substituting each amino acid in said set of amino acids at each variable position in each variant protein sequence," or "generating a probability matrix by combining said energetic fitness of each of said amino acids in each of said variant protein sequences for each of said protein backbone structures in said ensemble of related protein backbone structures to generate a total probability for each of said amino acids," as recited in amended claim 1. As such, the combination of MAYO with KOEHL cannot make claim 1 obvious or claims dependent therefrom.

Conclusion

The Applicant respectfully submits that all claims are in condition for allowance, which action is expeditiously requested. All amendments and cancellations are made without prejudice and disclaimer and may be made for reasons not explicitly stated or for reasons in addition to ones stated.

Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: 9 March 2006

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